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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,886	03/13/2000	David J. Grdina	P-01904US1	6435

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/523,886	GRDINA ET AL.	
	Examin r	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-13 and 23-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3-7,9-13 and 23-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 8-21-03 has been entered. Claim 34 has been added. Claims 1, 3-7, 9-13 and 23-34 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-7, 9-13 and 23-33 remain rejected and claim 34 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting or reducing the number of metastases in lung by administering WR-2721 at a concentration of 50mg/kg to 100mg/kg to an animal, does not reasonably provide enablement for reducing the number or inhibiting metastases in tissues other than lung or preventing metastases by administering any aminoalkylphosphorothioate or active metabolite thereof, or reducing the number of metastases by administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg or at a concentration between 100mg/kg to 150mg/kg to an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 5-19-03.

The newly added claim 34 specifies the dose is about 50 mg/kg to 100 mg/kg.

Applicants argue that the specification enables the present invention in different cancers and not just limited to lung, and the cited reference Kanclerz concerns

observations related to growth control after the cell has invaded the tissue but the present invention conerns the regulation of the invation not the growth of the cell post-invasion (amendment, p. 7, 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-19-03. Kanclerz implanted tumors into the tails of C57BL mice and surgically removed the tumor after the tumor reaches $40mm^3$, which results in the induction of spontaneous metastases. WR-2721 was administered 24 hrs after the surgery, therefore, the experiment is to test the effect of WR-2721 on the spontaneous metastases induced by the removal of the tumor in the mice. The development of spontaneous metastases was assessed by removing the lungs, rinsing in cold physiological saline, the lungs were weighed and fixed in Boulin's solution and metastases on the surfaces were scored with the aid of a dissecting microscope (p. 310, right column). Kanclerz reports that "Application of WR-2721 at a single dose of 0.4 g/kg had little or no effect on the incidence or number of LLC metastases. Multiple treatment with this radioprotector on 10 consecutive days at three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg) resulted in a small potentiation of pulmonary metastases formation (Table 5) (see p. 313, right column). Therefore, Kanclerz not only teaches measuring weight change of LLC and the incidence of metastases but also score the number of metastases on the lungs to determine the effect of WR-2721 on the spontaneous metastases. Thus, the teachings of Kanclerz is relevant to the present invention. Further, as discussed in the preceding Official action mailed 5-19-03, doses and schedules of a compound administered to a subject and the type of tumors and location of metastases are important factors in determining the effect of said compound on metastases. It was unpredictable at the time of the invention whether any

aminoalkylphosphorothioate or its active metabolite can reduce the number of metastases or inhibit metastases at locations other than lung in an animal. The specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed.

Applicants argue that in the present invention WR-2721 was administered on the first day following injection of the cells and the presence of cancer cells in the blood stream on in an established tumor are needed to test the inhibition of metastases but Kanclerz injected the cancer cells and waited for two weeks and treated the animal 24 hrs thereafter (amendment, p. 8-9).). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-19-03 and the reasons set forth above. Administration of WR-2721 on the first day **following** the injection of cancer cells still means that WR-2721 was administered **after** the injection of cells. As discussed above, in Kanclerz's experiment, WR-2721 was administered 24 hrs after the tumor was removed to induce spontaneous metastases, therefore, the experiment is to test the effect of WR-2721 on the spontaneous metastases induced by the removal of the tumor in the mice.

Applicants argue that the specification indicates that WR-2721 is exemplary of aminoalkylphosphorothioates and cites a number of US patents to support that (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-19-03 and the reasons set forth above. As discussed in the preceding Official action mailed 5-19-03, different radiosensitizer and radioprotector have different effects on spontaneous metastases and it was unpredictable at the time of the invention whether any aminoalkylphosphorothioate or its active metabolite other than WR-2721 can reduce the number of metastases or inhibit metastases at any location in an

animal. There is no evidence of record that aminoalkylphosphorothioates other than WR-2721 can reduce the number of metastases or inhibit metastases. The specification fails to provide sufficient enabling disclosure that aminoalkylphosphorothioates other than WR-2721 can reduce the number of metastases or inhibit metastases. Therefore, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that Kanclerz and Molas reference are irrelevant to the claimed invention and Milas describes a reduction in the enhancement of metastasesdue to the treatment of chemicals or radiation. Applicants further argue that examples 1 and 2 of the specification provide guidance for one or ordinary skill in the art to use the claimed invention and no undue experimentation is required (amendment, p. 10-11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-19-03 and the reasons set forth above. The rebuttal regarding Kanclerz is as discussed above. Milas teaches single dose of 400mg/kg WR-2721 greatly reduces radiation and CY-induced enhancement of metastases in the lung of mice. Although the teaching is related to chemicals or radiation, however, the experiment is associated with the effect of WR-2721 on the metastases simulated by the chemicals or radiation. Therefore, the cited reference Milas is relevant to the present invention. As discussed before, doses and schedules of a compound administered to a subject and the type of tumors and location of metastases are important factors in determining the effect of said compound on metastases, and it was unpredictable at the time of the invention what dosage of any aminoalkylphosphorothioate or its active metabolite would be sufficient to reduce the number of metastases or inhibit metastases at any location in an animal. Thus, one

skilled in the art at the time of the invention would require undue experimentation to practice over the scope of the invention claimed.

Applicants argue that the teachings of Gura has nothing to do with the present invention and the specification teaches effectiveness of a single dose of 50 mg/kg of WR-2721 for different tumor types and effect of multiple doses of WR-2721. Applicants further argue that proof of efficacy in clinical trials involving humans is not required for patentability and the claims are enabled for in vivo use (amendment, p. 12-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-19-03 and the reasons set forth above. The Office does not question the accuracy of the in vivo data disclosed in the specification. It should be noted that the rejection is directed to the **prevention** of metastases of various tumors *in vivo* by using any aminoalkylphosphorothioate and active metabolites thereof, such as WR-2721 and the reduction of the number of metastases in human. Preventing metastases in an animal means administration of the drug **before** infection or introduction of pathogen to said animal and said administration of the drug prevent the occurrence of metastases in said animal. The specification fails to provide enabling evidence that WR-2721 or any aminoalkylphosphorothioate at a concentration of 10mg/kg to 150mg/kg can **prevent** metastases at various locations in an animal. The teachings of Gura show that treating a mouse with drugs is different from treating a human with drugs. The in vivo data in mice can not extrapolated into success in human. The specification fails to provide sufficient enabling disclosure for reducing the number of metastases in a human exhibiting a primary tumor with a dose of 10 mg/kg to 150 mg/kg of an aminoalkylphosphorothioate

or active metabolite thereof. One skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.